

CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

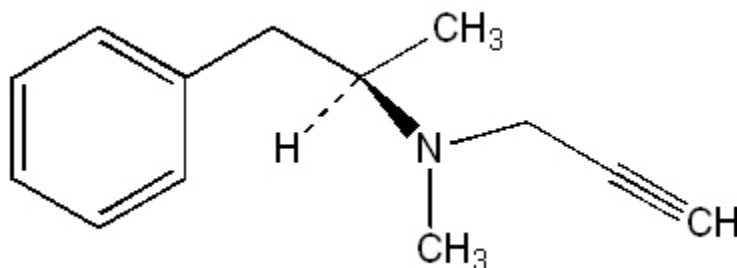
SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of EMSAM or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised for the need for close observation and communication with the prescriber. EMSAM is not approved for use in pediatric patients. Furthermore, EMSAM at any dose should not be used in children under the age of 12, even when administered with dietary modifications. (See **WARNINGS: Clinical Worsening and Suicide Risk**, **PRECAUTIONS: Information for Patients**, and **PRECAUTIONS: Pediatric Use**.)

DESCRIPTION

EMSAM[®] (selegiline transdermal system) is a transdermally administered antidepressant. When applied to intact skin, **EMSAM** is designed to continuously deliver selegiline over a 24-hour period.

Selegiline base is a colorless to yellow liquid, chemically described as (-)-(N)-Methyl-N-[(1R)-1-methyl-2-phenylethyl]prop-2-yn-1-amine. It has an empirical formula of C₁₃H₁₇N and a molecular weight of 187.30. The structural formula is:



Selegiline Base

EMSAM systems are transdermal patches that contain 1 mg of selegiline per cm² and deliver approximately 0.3 mg of selegiline per cm² over 24 hours. **EMSAM** systems are available in three sizes: 20 mg/20 cm², 30 mg/30 cm², and 40 mg/40 cm² that deliver, on average, doses of 6 mg, 9 mg, or 12 mg, respectively, of selegiline over 24 hours.

EMSAM is a matrix-type transdermal system composed of three layers as illustrated in Figure 1 below. Layer 1 is the Backing Film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 is the Adhesive/Drug Layer. Layer 3 consists of side-by-side release liners that are peeled off and discarded by the patient prior to applying **EMSAM**. The inactive ingredients are acrylic adhesive, ethylene vinyl acetate/polyethylene, polyester, polyurethane, and silicone coated polyester.

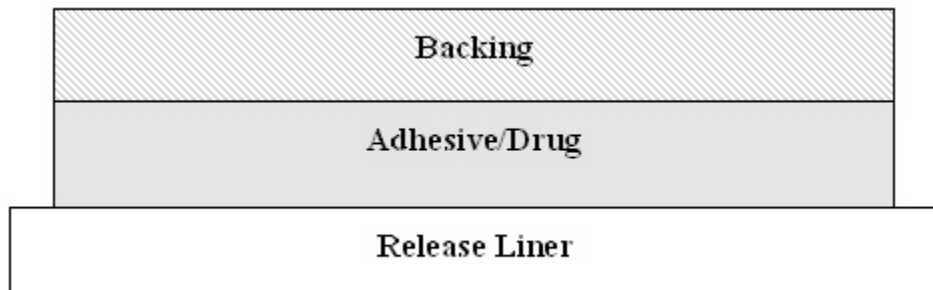


Figure 1: Side view of EMSAM system. (Not to scale.)

CLINICAL PHARMACOLOGY

Pharmacodynamics

Selegiline (the drug substance of **EMSAM**) is an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline has a greater affinity for MAO-B, compared to MAO-A. However, at antidepressant doses, selegiline inhibits both isoenzymes (see below).

The mechanism of action of **EMSAM** as an antidepressant is not fully understood, but is presumed to be linked to potentiation of monoamine neurotransmitter activity in the central nervous system (CNS) resulting from its inhibition of MAO activity. In an *in vivo* animal model used to test for antidepressant activity (Forced Swim Test), selegiline administered by transdermal patch exhibited antidepressant properties only at doses that inhibited both MAO-A and MAO-B activity in the brain. In the CNS, MAO-A and MAO-B play important roles in the catabolism of neurotransmitter amines such as norepinephrine, dopamine, and serotonin, as well as neuromodulators such as phenylethylamine. Other molecular sites of action have also been explored and in this regard, a direct pharmacological interaction may also occur between selegiline and brain neuronal α_{2B} receptors. In *in vitro* receptor binding assays, selegiline has demonstrated affinity for the human recombinant adrenergic α_{2B} receptor ($K_i = 284 \mu\text{M}$). No affinity [$K_i > 10 \mu\text{M}$] was noted at dopamine receptors, adrenergic β_3 , glutamate, muscarinic M_1 - M_5 , nicotinic, or rolipram receptor/sites.

Pharmacokinetics

Absorption

Following dermal application of **EMSAM** to humans, 25% - 30% of the selegiline content on average is delivered systemically over 24 hours (range ~ 10% - 40%). Consequently, the degree of drug absorption may be 1/3 higher than the average amounts of 6 mg to 12 mg per 24 hours. Transdermal dosing results in substantially higher exposure to selegiline and lower exposure to metabolites compared to oral dosing, where extensive first-pass metabolism occurs (Figure 2). In a 10-day study with **EMSAM** administered to normal volunteers, steady-state selegiline plasma concentrations were achieved within 5 days of daily dosing. Absorption of selegiline is similar when **EMSAM** is applied to the upper torso or upper thigh. Mean (95% CI) steady-state plasma concentrations in healthy men and women following application of **EMSAM** to the upper torso or upper thigh are shown in Figure 3.

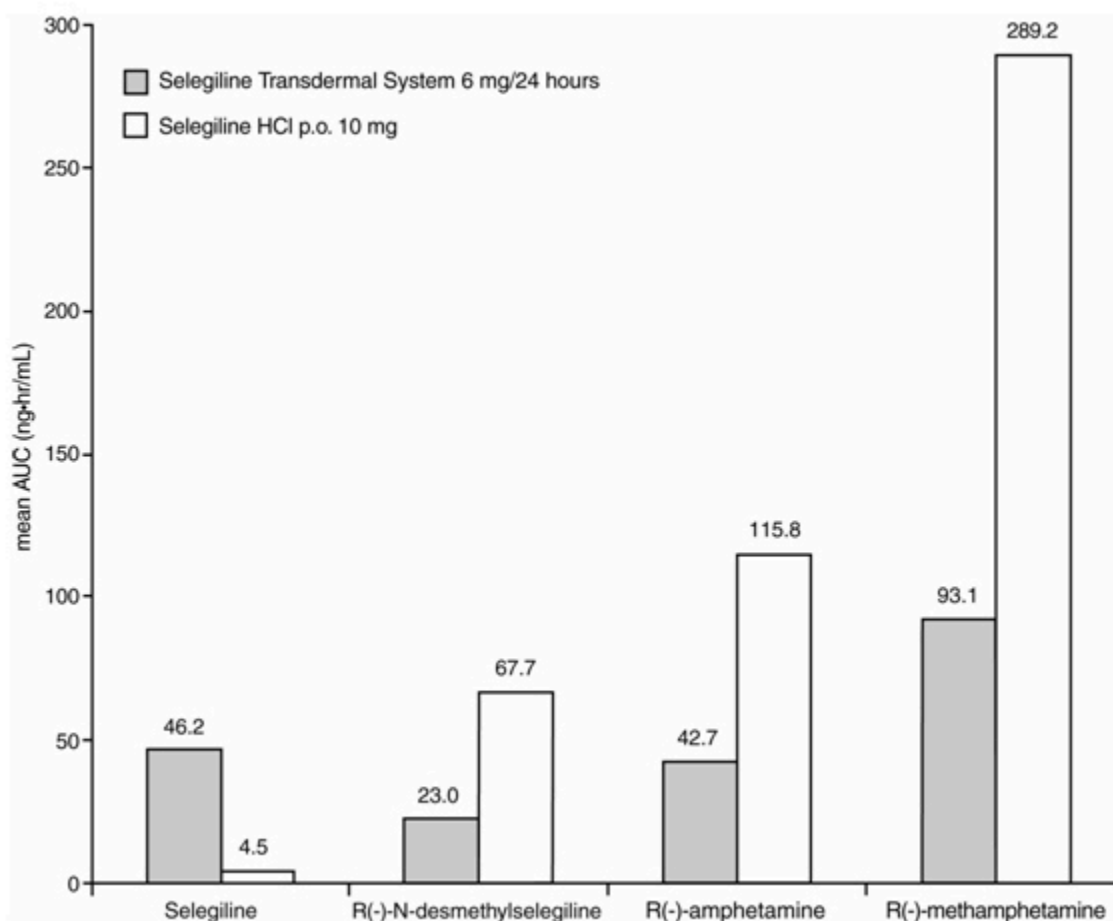


Figure 2: Average AUC_{inf} (ng•hr/mL) of selegiline and the three major metabolites estimated for a single, 24-hour application of an EMSAM 6 mg/24 hours patch and a single, 10 mg oral immediate release dose of selegiline HCl in 12 healthy male and female volunteers.

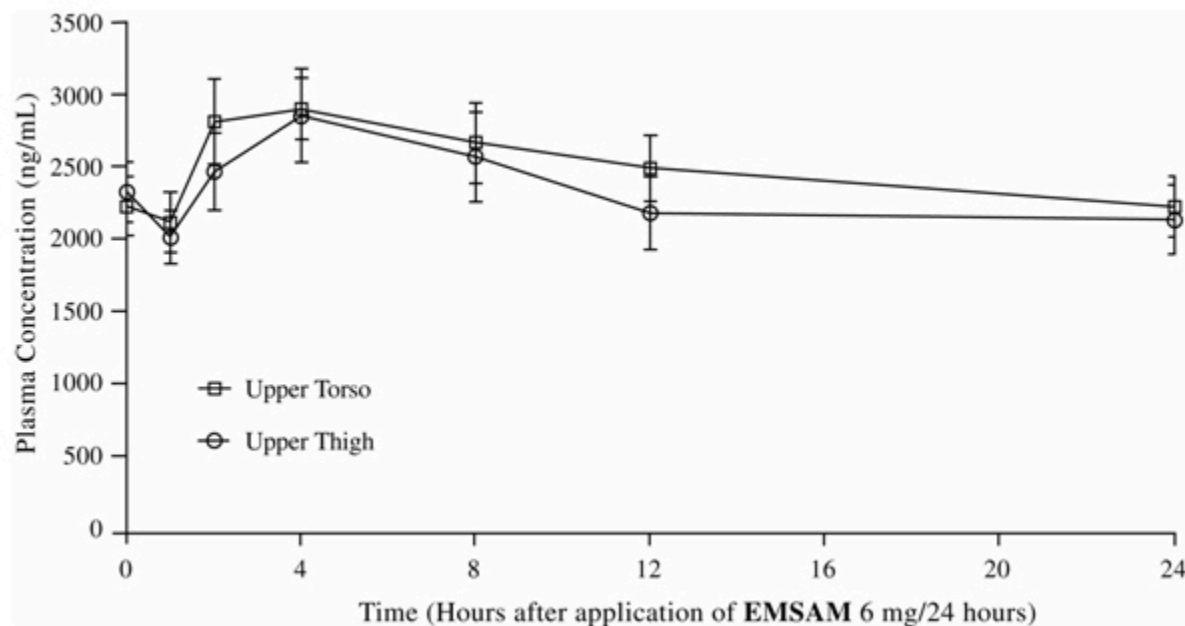


Figure 3: Average plasma (\pm 95% CI) selegiline concentrations in healthy male and female volunteers at steady-state after application of EMSAM 6 mg/24 hours to the upper torso.

Distribution

Following dermal application of radiolabeled selegiline to laboratory animals, selegiline is rapidly distributed to all body tissues. Selegiline rapidly penetrates the blood-brain barrier.

In humans, selegiline is approximately 90% bound to plasma protein over a 2 - 500 ng/mL concentration range. Selegiline does not accumulate in the skin.

In vivo Metabolism

Transdermally absorbed selegiline (via **EMSAM**) is not metabolized in human skin and does not undergo extensive first-pass metabolism. Selegiline is extensively metabolized by several CYP₄₅₀-dependent enzyme systems (see *In vitro* Metabolism). Selegiline is metabolized initially via N-dealkylation or N-depropargylation to form N-desmethylselegiline or R(-)-methamphetamine, respectively. Both of these metabolites can be further metabolized to R(-)-amphetamine. These metabolites are all levorotatory (l)-enantiomers and no racemic biotransformation to the dextrorotatory form (i.e., S(+)-amphetamine or S(+)-methamphetamine) occurs. R(-)-methamphetamine and R(-)-amphetamine are mainly excreted unchanged in urine.

In vitro Metabolism

In vitro studies utilizing human liver microsomes demonstrated that several CYP₄₅₀-dependent enzymes are involved in the metabolism of selegiline and its metabolites. CYP2B6, CYP2C9, and CYP3A4/5 appeared to be the major contributing enzymes in the formation of R(-)-methamphetamine from selegiline, with CYP2A6 having a minor role. CYP2A6, CYP2B6, and CYP3A4/5 appeared to contribute to the formation of R(-)-amphetamine from N-desmethylselegiline.

The potential for selegiline or N-desmethylselegiline to inhibit individual CYP₄₅₀-dependent enzyme pathways was also examined *in vitro* with human liver microsomes. Each substrate was examined over a concentration range of 2.5 to 250 μ M. Consistent with competitive inhibition, both selegiline and N-desmethylselegiline caused a concentration dependent inhibition of CYP2D6 at 10 - 250 μ M and CYP3A4/5 at 25 - 250 μ M. CYP2C19 and CYP2B6 were also inhibited at concentrations \geq 100 μ M. All inhibitory effects of selegiline and N-desmethylselegiline occurred at concentrations that are several orders of magnitude higher than concentrations seen clinically (highest predose concentration observed at a dose of 12 mg/24 hours at steady-state was 0.046 μ M) (see PRECAUTIONS, Drug Interactions).

Excretion

Approximately 10% and 2% of a radiolabeled dose applied dermally, as a DMSO solution, was recovered in urine and feces respectively, with at least 63% of the dose remaining unabsorbed. The remaining 25% of the dose was unaccounted for. Urinary excretion of unchanged selegiline accounted for 0.1% of the applied dose with the remainder of the dose recovered in urine being metabolites.

The systemic clearance of selegiline after intravenous administration was 1.4 L/min, and the mean half-lives of selegiline and its three metabolites, R(-)-N-desmethyloselegiline, R(-)-amphetamine, and R(-)-methamphetamine, ranged from 18 - 25 hours.

Population Subgroups

Age -- The effect of age on the pharmacokinetics or metabolism of selegiline during administration of **EMSAM** has not been systematically evaluated. The recommended dose for elderly patients is **EMSAM** 6 mg/24 hours. (See **DOSAGE AND ADMINISTRATION**.)

Gender -- No gender differences have been observed in the pharmacokinetics or metabolism of selegiline during administration of **EMSAM**. No adjustment of **EMSAM** dosage based on gender is needed.

Reduced Hepatic Function

After a single administration of **EMSAM** 6 mg/24 hours in 8 patients with mild or moderate liver impairment (Child-Pugh classifications of A or B), no differences in either the metabolism or pharmacokinetic behavior of selegiline or its metabolites were observed as compared with data of normal subjects. No adjustment of **EMSAM** dosage is required in patients with moderate liver impairment.

Reduced Renal Function

Data from a single dose study examining the pharmacokinetics of **EMSAM** 6 mg/24 hours in 12 patients with renal impairment suggest that mild, moderate, or severe renal impairment does not affect the pharmacokinetics of selegiline after transdermal application. Therefore, no adjustment of **EMSAM** dosage is required in patients with renal impairment.

Dermal Adhesion

Dermal adhesion of **EMSAM** was examined after application of 6 mg/24 hours selegiline patches for 10 days to the upper torso. Approximately 88% - 89% of 6 mg/24 hours selegiline patches applied to the upper torso exhibited < 10% lift with approximately 6% - 7% of patches becoming detached.

External Heat

The effect of direct heat applied to the **EMSAM** patch on the bioavailability of selegiline has not been studied. However, in theory, heat may result in an increase in the amount of selegiline absorbed from the **EMSAM** patch and produce elevated serum levels of selegiline. Patients should be advised to avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Clinical Efficacy Trials

The efficacy of **EMSAM** as a treatment for major depressive disorder was established in two placebo-controlled studies of 6 and 8 weeks duration in adult outpatients (ages 18 to 70 years) meeting DSM-IV criteria for major depressive disorder. In both studies, patients were randomized to double-blind treatment with **EMSAM** or placebo. The 6-week trial (N = 176) showed that **EMSAM** 6 mg/24 hours was significantly more effective than placebo on the 17-item Hamilton Depression Rating Scale (HAM-D). In an 8-week dose titration trial, depressed patients (N = 265), who received **EMSAM** or placebo at a starting dose of 6 mg/24 hours, with possible increases to 9 mg/24 hours or 12 mg/24 hours based on clinical response, showed significant improvement compared with placebo on the primary outcome measure, the 28-item HAM-D total score.

In another trial, 322 patients meeting DSM-IV criteria for major depressive disorder who had responded during an initial 10-week open-label treatment phase for about 25 days, on average, to **EMSAM** 6 mg/24 hours were randomized either to continuation of **EMSAM** at the same dose (N = 159) or to placebo (N = 163) under double-blind conditions for observation of relapse. About 52% of the **EMSAM**-treated patients, as well as about 52% of the placebo-treated patients, had discontinued treatment by week 12 of the double-blind phase. Response during the open-label phase was defined as 17-item HAM-D score < 10 at either week 8 or 9 and at week 10 of the open-label phase. Relapse during the double-blind phase was defined as follows: (1) a 17-item HAM-D score \geq 14, (2) a CGI-S score of \geq 3 (with at least a 2-point increase from double-blind baseline), and (3) meeting DSM-IV criteria for major depressive disorder on two consecutive visits \geq 11 days apart. In the double-blind phase, patients receiving continued **EMSAM** experienced a significantly longer time to relapse.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

INDICATIONS AND USAGE

EMSAM (selegiline transdermal system) is indicated for the treatment of major depressive disorder.

The efficacy of **EMSAM** in the treatment of major depressive disorder was established in 6- and 8-week placebo-controlled trials of outpatients with diagnoses of DSM-IV category of major depressive disorder (see Clinical Efficacy Trials).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicide attempt or suicidal ideation.

The benefit of maintaining patients with major depressive disorder on therapy with **EMSAM** after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see Clinical Efficacy Trials under CLINICAL PHARMACOLOGY). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

The antidepressant action of **EMSAM** in hospitalized depressed patients has not been studied.

CONTRAINDICATIONS

EMSAM (selegiline transdermal system) is contraindicated in patients with known hypersensitivity to selegiline or to any component of the transdermal system.

EMSAM (selegiline transdermal system) is contraindicated with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, and paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan; St. John’s wort; mirtazapine; and cyclobenzaprine. **EMSAM** should not be used with oral selegiline or other MAO inhibitors (MAOIs e.g., isocarboxazid, phenelzine, and tranlycypromine) (see WARNINGS).

Carbamazepine and oxcarbazepine are contraindicated in patients taking selegiline (see PRECAUTIONS, Drug Interactions).

As with other MAOIs, **EMSAM** is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

As with other MAOIs, patients taking **EMSAM** should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. **EMSAM** should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

As with other MAOIs, **EMSAM** is contraindicated for use in patients with pheochromocytoma.

EMSAM is an irreversible MAO inhibitor. As a class, these compounds have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours.** (See WARNINGS and PRECAUTIONS, Drug Interactions, Tyramine.)

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorders (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressants in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

AGE RANGE	DRUG-PLACEBO DIFFERENCE IN
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	NUMBER OF CASES OF SUICIDALITY PER 1,000 PATIENTS TREATED
	Increases Compared to Placebo
< 18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. **There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.**

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Due to the limited data, EMSAM at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. EMSAM is not approved for use in pediatric patients (See PRECAUTIONS: Pediatric Use).

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for EMSAM should be written for the smallest quantity of patches consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that EMSAM is not approved for use in treating bipolar depression.

Hypertensive Crisis

EMSAM is an irreversible MAO inhibitor. MAO is important in the catabolism of dietary amines (e.g., tyramine). In this regard, significant inhibition of intestinal MAO-A activity can impose a cardiovascular safety risk following the ingestion of tyramine-rich foods. As a class, MAOIs have been associated with hypertensive crises caused by the ingestion of foods with a high concentration of tyramine.

Hypertensive crises, which in some cases may be fatal, are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Intracranial bleeding has been reported in association with the increase in blood pressure. Patients should be instructed as to the signs and symptoms of severe hypertension and advised to seek immediate medical attention if these signs or symptoms are present.

In 6 of the 7 clinical studies conducted with EMSAM at doses of 6 mg/24 hours - 12 mg/24 hours, patients were not limited to a modified diet typically associated with this class of compounds. Although no hypertensive crises were reported as part of the safety

assessment, the likelihood of developing this reaction cannot be fully determined since the amount of tyramine typically consumed during the course of treatment is not known and blood pressure was not continuously monitored.

To further define the likelihood of hypertensive crises with use of **EMSAM**, several Phase I tyramine challenge studies were conducted both with and without food (see PRECAUTIONS, Drug Interactions, Tyramine). In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours, and the results from the Phase I tyramine challenge study in fed volunteers administered **EMSAM** 12 mg/24 hours (see PRECAUTIONS, Drug Interactions, Tyramine), patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours.**

If a hypertensive crisis occurs, **EMSAM** should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Phentolamine 5 mg or labetalol 20 mg administered slowly intravenously is recommended therapy to control hypertension. Alternately, nitroprusside delivered by continuous intravenous infusion may be used. Fever should be managed by means of external cooling. Patients must be closely monitored until symptoms have stabilized.

Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours

The following foods and beverages should be avoided beginning on the first day of **EMSAM** 9 mg/24 hours or 12 mg/24 hours treatment, and should continue to be avoided for 2 weeks after a dose reduction to **EMSAM** 6 mg/24 hours or following the discontinuation of **EMSAM** 9 mg/24 hours or 12 mg/24 hours.

Food and beverages to avoid and those which are acceptable¹:

Class of Food and Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods and Drinks, Containing No or Little Tyramine
<u>Meat, Poultry, and Fish</u>	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring, and any spoiled or improperly stored meat, poultry, and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry, and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
<u>Vegetables</u>	Broad bean pods (fava bean pods)	All other vegetables
<u>Dairy</u>	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese, and yogurt
<u>Beverages</u>	All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation	As with other antidepressants, concomitant use of alcohol with EMSAM is not recommended. (Bottled and canned beers and wines contain little or no tyramine.)
<u>Miscellaneous</u>	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu), OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

¹
Adapted from K.I. Shulman, S.E. Walker, Psychiatric Annals 2001; 31:378-384

Use With Other Drugs Affecting Monoamine Activity

Serious, sometimes fatal, central nervous system (CNS) toxicity referred to as the "serotonin syndrome" has been reported with the combination of non-selective MAOIs with certain other drugs, including tricyclic or selective serotonin reuptake inhibitor antidepressants, amphetamines, meperidine, or pentazocine. Serotonin syndrome is characterized by signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Similar less severe syndromes have been reported in a few patients receiving a combination of oral selegiline with one of these agents.

Therefore, **EMSAM** (selegiline transdermal system) should not be used in combination with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranylcypromine); mirtazapine; bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan; or St. John's wort because of the risk of life-threatening adverse reactions. Also, **EMSAM** should not be used with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine). (See CONTRAINDICATIONS.)

Concomitant use of **EMSAM** with buspirone hydrochloride is not advised since several cases of elevated blood pressure have been reported in patients taking MAOIs who were then given buspirone HCl.

After stopping treatment with SSRIs; SNRIs; TCAs; MAOIs; meperidine and analgesics such as tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; mirtazapine; bupropion HCl; or buspirone HCl, a time period equal to 4 - 5 half-lives (approximately 1 week) of the drug or any active metabolite should elapse before starting therapy with **EMSAM**. Because of the long half-life of fluoxetine and its active metabolite, at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with **EMSAM**. At least 2 weeks should elapse after stopping **EMSAM** before starting therapy with buspirone HCl or a drug that is contraindicated with **EMSAM**.

PRECAUTIONS

General

Hypotension

As with other MAOIs, postural hypotension, sometimes with orthostatic symptoms, can occur with **EMSAM** therapy. In short-term, placebo-controlled depression studies, the incidence of orthostatic hypotension (i.e., a decrease of 10 mmHg or greater in mean blood pressure when changing position from supine or sitting to standing) was 9.8% in **EMSAM**-treated patients and 6.7% in placebo-treated patients. It is recommended that elderly patients treated with **EMSAM** be closely observed for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with pre-existing orthostasis. Postural hypotension may be relieved by having the patient recline until the symptoms have abated. Patients should be cautioned to change positions gradually. Patients displaying orthostatic symptoms should have appropriate dosage adjustments as warranted.

Activation of Mania/Hypomania

During Phase III trials, a manic reaction occurred in 8/2036 (0.4%) patients treated with **EMSAM**. Activation of mania/hypomania can occur in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, **EMSAM** should be used cautiously in patients with a history of mania.

Use in Patients With Concomitant Illness

Clinical experience with **EMSAM** in patients with certain concomitant systemic illnesses is limited. Caution is advised when using **EMSAM** in patients with disorders or conditions that can produce altered metabolism or hemodynamic responses.

EMSAM has not been systematically evaluated in patients with a history of recent myocardial infarction or unstable heart disease. Such patients were generally excluded from clinical studies during the product's premarketing testing.

No ECG abnormalities attributable to **EMSAM** were observed in clinical trials.

Although studies of phenylpropanolamine and pseudoephedrine did not reveal pharmacokinetic drug interactions with **EMSAM**, it is prudent to avoid the concomitant use of sympathomimetic agents, such as some decongestants.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with **EMSAM** and should counsel them in its appropriate use. A patient **Medication Guide** about "**Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions**" is available for **EMSAM**. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking **EMSAM**.

Clinical Worsening and Suicide Risk

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment or when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly change in the medication.

General

Patients should be advised not to use oral selegiline while on **EMSAM** therapy.

Patients should be advised not to use carbamazepine or oxcarbazepine while on **EMSAM** therapy.

Patients should be advised not to use meperidine and analgesic agents such as tramadol, methadone, and propoxyphene.

Patients should be advised not to use sympathomimetic agents while on **EMSAM** therapy.

Patients should be advised not to use selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine, and St. John's wort), dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline), mirtazapine, oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranylcypromine), bupropion hydrochloride or buspirone hydrochloride while on **EMSAM** therapy.

EMSAM (selegiline transdermal system) has not been shown to impair psychomotor performance; however, any psychoactive drug may potentially impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that **EMSAM** therapy does not impair their ability to engage in such activities.

Patients should be told that, although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol, the concomitant use of **EMSAM** and alcohol in depressed patients is not recommended.

Patients should be advised to notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbals, because of the potential for drug interactions. Patients should also be advised to avoid tyramine-containing nutritional supplements and any cough medicine containing dextromethorphan.

Patients should be advised to use **EMSAM** exactly as prescribed. The need for dietary modifications at higher doses should be explained, and a brief description of hypertensive crisis provided. Rare hypertensive reactions with oral selegiline at doses recommended for Parkinson's disease and associated with dietary influences have been reported. The clinical relevance to **EMSAM** is unknown.

Patients should be advised that certain tyramine-rich foods and beverages should be avoided while on **EMSAM** 9 mg/24 hours or **EMSAM** 12 mg/24 hours, and for 2 weeks following discontinuation of **EMSAM** at these doses (see CONTRAINDICATIONS and WARNINGS).

Patients should be instructed to immediately report the occurrence of the following acute symptoms: severe headache, neck stiffness, heart racing or palpitations, or other sudden or unusual symptoms.

Patients should be advised to avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight since heat may result in an increase in the amount of selegiline absorbed from the **EMSAM** patch and produce elevated serum levels of selegiline.

Patients should be advised to change position gradually if lightheaded, faint, or dizzy while on **EMSAM** therapy.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during **EMSAM** therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

While patients may notice improvement with **EMSAM** therapy in 1 to several weeks, they should be advised of the importance of continuing drug treatment as directed.

Patients should be advised not to cut the **EMSAM** system into smaller portions.

For instructions on how to use **EMSAM**, see DOSAGE AND ADMINISTRATION, How to Use EMSAM.

Drug Interactions

The potential for drug interactions between **EMSAM** and a variety of drugs was examined in several human studies. Drug interaction studies described below were conducted with **EMSAM** 6 mg/24 hours. Although no differences are expected, drug interaction studies have not been conducted at higher doses (see In vitro Metabolism). In all of the studies described below, no drug-related adverse events were noted that required discontinuation of any subjects. Further, the incidence and nature of the adverse events were consistent with those known for selegiline or the test agent.

Alcohol

The pharmacokinetics and pharmacodynamics of alcohol (0.75 mg/kg) alone or in combination with **EMSAM** 6 mg/24 hours for 7 days of treatment was examined in 16 healthy volunteers. No clinically significant differences were observed in the pharmacokinetics or pharmacodynamics of alcohol or the pharmacokinetics of selegiline during co-administration. Although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol (0.75 mg/kg) and failed to alter the pharmacokinetic properties of alcohol, patients should be advised that the use of alcohol is not recommended while taking **EMSAM**.

Alprazolam

In subjects who had received **EMSAM** 6 mg/24 hours for 7 days, co-administration with alprazolam (15 mg/day), a CYP3A4/5 substrate, did not affect the pharmacokinetics of either selegiline or alprazolam.

Carbamazepine

Carbamazepine is an enzyme inducer and typically causes decreases in drug exposure; however, slightly increased levels of selegiline and its metabolites were seen after single application of **EMSAM** 6 mg/24 hours in subjects who had received carbamazepine (400 mg/day) for 14 days. Changes in plasma selegiline concentrations were nearly two-fold, and variable across the subject population. The clinical relevance of these observations is unknown. Carbamazepine is contraindicated with MAOIs, including selegiline (see CONTRAINDICATIONS).

Ibuprofen

In subjects who had received **EMSAM** 6 mg/24 hours for 11 days, combined administration with the CYP2C9 substrate ibuprofen (800 mg single dose) did not affect the pharmacokinetics of either selegiline or ibuprofen.

Ketoconazole

Seven-day treatment with ketoconazole (200 mg/day), a potent inhibitor of CYP3A4, did not affect the steady-state pharmacokinetics of selegiline in subjects who received **EMSAM** 6 mg/24 hours for 7 days and no differences in the pharmacokinetics of ketoconazole were observed.

Levothyroxine

In healthy subjects who had received **EMSAM** 6 mg/24 hours for 10 days, single dose administration with levothyroxine (150 µg) did not alter the pharmacokinetics of either selegiline or levothyroxine (as judged by T₃ and T₄ plasma levels).

Olanzapine

In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with olanzapine, a substrate for CYP1A2, CYP2D6, and possibly CYP2A6, did not affect the pharmacokinetics of either selegiline or olanzapine.

Phenylpropanolamine (PPA)

In subjects who had received **EMSAM** 6 mg/24 hours for 9 days, co-administration with PPA (25 mg every 4 hours for 24 hours) did not affect the pharmacokinetics of PPA. There was a higher incidence of significant blood pressure elevations with the co-administration of **EMSAM** and PPA than with PPA alone, suggesting a possible pharmacodynamic interaction. It is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Pseudoephedrine

EMSAM 6 mg/24 hours for 10 days, co-administered with pseudoephedrine (60 mg, 3 times a day) did not affect the pharmacokinetics of pseudoephedrine. The effect of pseudoephedrine on **EMSAM** was not examined. There were no clinically significant changes in blood pressure during pseudoephedrine administration alone, or in combination with **EMSAM**. Nonetheless, it is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Risperidone

In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with risperidone (2 mg per day for 7 days), a substrate for CYP2D6, did not affect the pharmacokinetics of either selegiline or risperidone.

Tyramine

Selegiline (the drug substance of **EMSAM**) is an irreversible inhibitor of monoamine oxidase (MAO), a ubiquitous intracellular enzyme. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline shows greater affinity for MAO-B; however, as selegiline concentration increases, this selectivity is lost with resulting dose-related inhibition of MAO-A. Intestinal MAO is predominantly type A, while in the brain both isoenzymes exist.

MAO plays a vital physiological role in terminating the biological activity of both endogenous and exogenous amines. In addition to their role in the catabolism of monoamines in the CNS, MAOs are also important in the catabolism of exogenous amines found in a variety of foods and drugs. MAO in the gastrointestinal tract (primarily type A) provides protection from exogenous amines with vasopressor actions, such as tyramine, which if absorbed intact can cause a hypertensive crisis, the so-called "cheese reaction." If a large amount of tyramine is absorbed systemically, it is taken up by adrenergic neurons and causes norepinephrine release from neuronal storage sites with resultant elevation of blood pressure. While most foods contain negligible amounts or no tyramine, a few food products (see WARNINGS) may contain large amounts of tyramine that represent a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAOIs. Tyramine-containing nutritional supplements should be avoided by patients taking **EMSAM** (selegiline transdermal system).

Animal studies have indicated the transdermal administration of selegiline via **EMSAM** 6 mg/24 hours allows for critical levels of MAO inhibition to be achieved in the brain while avoiding levels of gastrointestinal inhibition. To further define the risk of hypertensive crises with use of **EMSAM**, several Phase I tyramine challenge studies were conducted both with and without food.

Fourteen tyramine challenge studies including 214 healthy subjects (age range 18 - 65; 31 subjects > 50 years of age) were conducted to determine the pressor effects of oral tyramine with concurrent **EMSAM** treatment (6 mg/24 hours - 12 mg/24 hours), measured as the dose of tyramine required to raise systolic blood pressure by 30 mmHg (TYR30). Studies were conducted with and without concomitant administration of food. Studies conducted with food are most relevant to clinical practice since tyramine typically will be consumed in food. A high-tyramine meal is considered to contain up to 40 mg of tyramine.

One study using a crossover design in 13 subjects investigated tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours and oral selegiline (5 mg twice daily) for 9 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 338 mg and 385 mg in subjects treated with **EMSAM** and oral selegiline, respectively.

Another study using a crossover design in 10 subjects investigated tyramine pressor doses after administration of **EMSAM** 6 mg/24 hours or tranlycypromine 30 mg/day for 10 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 270 mg in subjects treated with **EMSAM** 6 mg/24 hours and 10 mg in subjects treated with tranlycypromine.

In a third crossover study, tyramine without food was administered to 12 subjects. The mean tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours for 9 and 33 days were 292 mg and 204 mg, respectively. The lowest pressor dose was 50 mg in one subject in the 33-day group.

Tyramine pressor doses were also studied in 11 subjects after extended treatment with **EMSAM** 12 mg/24 hours. At 30, 60, and 90 days, the mean pressor doses (TYR30) of tyramine administered without food were 95 mg, 72 mg, and 88 mg, respectively. The lowest pressor dose without food was 25 mg in 3 subjects at day 30 while on **EMSAM** 12 mg/24 hours. Eight subjects from this study, with a mean tyramine pressor dose of 64 mg at 90 days, were subsequently administered tyramine with food, resulting in a mean pressor dose of 172 mg (2.7 times the mean pressor dose observed without food, $p < 0.003$).

With the exception of one study (N = 153), the Phase III clinical development program was conducted without requiring a modified diet (N = 2553, 1606 at 6 mg/24 hours, and 947 at 9 mg/24 hours or 12 mg/24 hours). No hypertensive crises were reported in any patient receiving **EMSAM**.

In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours.** (See WARNINGS.)

Warfarin

Warfarin is a substrate for CYP2C9 and CYP3A4 metabolism pathways. In healthy volunteers titrated with Coumadin® (warfarin sodium) to clinical levels of anticoagulation (INR of 1.5 to 2), co-administration with **EMSAM** 6 mg/24 hours for 7 days did not affect the pharmacokinetics of the individual warfarin enantiomers. **EMSAM** did not alter the clinical pharmacodynamic effects of warfarin as measured by INR, Factor VII or Factor X levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In an oral carcinogenicity study in rats, selegiline given in the diet for 104 weeks was not carcinogenic up to the highest evaluable dose tested (3.5 mg/kg/day, which is 3 times the oral maximum recommended human dose on a mg/m^2 basis).

Carcinogenicity studies have not been conducted with transdermal administration of selegiline.

Mutagenesis

Selegiline induced mutations and chromosomal damage when tested in the *in vitro* mouse lymphoma assay with and without metabolic activation. Selegiline was negative in the Ames assay, the *in vitro* mammalian chromosome aberration assay in human lymphocytes, and the *in vivo* oral mouse micronucleus assay.

Impairment of Fertility

A mating and fertility study was conducted in male and female rats at transdermal doses of 10, 30, and 75 mg/kg/day of selegiline (8, 24, and 60 times the maximum recommended human dose of **EMSAM** [12 mg/24 hours] on a mg/m^2 basis). Slight decreases in sperm concentration and total sperm count were observed at the high dose; however, no significant adverse effects on fertility or reproductive performance were observed.

Teratogenic Effects - Pregnancy Category C

In an embryofetal development study in rats, dams were treated with transdermal selegiline during the period of organogenesis at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the maximum recommended human dose [MRHD] of **EMSAM** [12 mg/24 hours] on a mg/m^2 basis). At the highest dose there was a decrease in fetal weight and slight increases in malformations, delayed ossification (also seen at the mid dose), and embryofetal post-implantation lethality. Concentrations of selegiline and its metabolites in fetal plasma were generally similar to those in maternal plasma. In an *oral* embryofetal development study in rats, a decrease in fetal weight occurred at the highest dose tested (36 mg/kg; no-effect dose 12 mg/kg); no increase in malformations was seen.

In an embryofetal development study in rabbits, dams were treated with transdermal selegiline during the period of organogenesis at doses of 2.5, 10, and 40 mg/kg/day (4, 16, and 64 times the MRHD on a mg/m^2 basis). A slight increase in visceral malformations was

seen at the high dose. In an *oral* embryofetal development study in rabbits, increases in total resorptions and post-implantation loss, and a decrease in the number of live fetuses per dam, occurred at the highest dose tested (50 mg/kg; no-effect dose 25 mg/kg). In a prenatal and postnatal development study in rats, dams were treated with transdermal selegiline at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the MRHD on a mg/m² basis) on days 6 - 21 of gestation and days 1 - 21 of the lactation period. An increase in post-implantation loss was seen at the mid and high doses, and an increase in stillborn pups was seen at the high dose. Decreases in pup weight (throughout lactation and post-weaning periods) and survival (throughout lactation period), retarded pup physical development, and pup epididymal and testicular hypoplasia, were seen at the mid and high doses. Retarded neurobehavioral and sexual development was seen at all doses. Adverse effects on pup reproductive performance, as evidenced by decreases in implantations and litter size, were seen at the high dose. These findings suggest persistent effects on the offspring of treated dams. A no-effect dose was not established for developmental toxicity. In this study, concentrations of selegiline and its metabolites in milk were ~ 15 and 5 times, respectively, the concentrations in plasma, indicating that the pups were directly dosed during the lactation period.

There are no adequate and well-controlled studies in pregnant women. **EMSAM** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of **EMSAM** on labor and delivery in humans is unknown.

Nursing Mothers

In a prenatal and postnatal study of transdermal selegiline in rats, selegiline and metabolites were excreted into the milk of lactating rats. The levels of selegiline and metabolites in milk were approximately 15 and 5 times, respectively, steady-state levels of selegiline and metabolites in maternal plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised administering **EMSAM** to a nursing mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk).

Anyone considering the use of **EMSAM** (selegiline transdermal system) in a child or adolescent must balance the potential risks with the clinical need.

Due to limited data, **EMSAM** at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. **EMSAM** is not approved for use in pediatric patients.

Commercially available doses of **EMSAM** have not been studied in children under the age of 12 years. Limited pharmacokinetic data with lower doses than in the commercially available formulations suggest that children under the age of 12 years treated with **EMSAM** may be exposed to increased levels of selegiline compared to adolescents or adults. Therefore, the possibility exists for an increased risk of hypertensive crisis, even at the lowest dose of commercially available **EMSAM**, when administered without dietary modifications.

Geriatric Use

One hundred ninety-eight (198) elderly (≥ 65 years of age) patients participated in clinical studies with **EMSAM** 6 mg/24 hours to 12 mg/24 hours. There were no overall differences in effectiveness between elderly and younger patients. In short-term, placebo-controlled depression trials, patients age 50 and older appeared to be at higher risk for rash (4.4% **EMSAM** vs. 0% placebo) than younger patients (3.4% **EMSAM** vs. 2.4% placebo).

ADVERSE EVENTS

The premarketing development program for **EMSAM** included selegiline exposures in patients and/or normal subjects from two different groups of studies: 702 healthy subjects in clinical pharmacology/pharmacokinetics studies and 2036 exposures from patients in controlled and uncontrolled major depressive disorder clinical trials. The conditions and duration of treatment with **EMSAM** varied and included double-blind, open-label, fixed-dose, and dose titration studies of short-term and longer-term exposures. Safety was assessed by monitoring adverse events, physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term Placebo-Controlled Trials

Adverse Events Associated with Discontinuation of Treatment

Among 817 depressed patients who received **EMSAM** at doses of either 3 mg/24 hours (151 patients), 6 mg/24 hours (550 patients) or 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours (116 patients) in placebo-controlled trials of up to 8 weeks in duration, 7.1%

discontinued treatment due to an adverse event as compared with 3.6% of 668 patients receiving placebo. The only adverse event associated with discontinuation, in at least 1% of **EMSAM**-treated patients at a rate at least twice that of placebo, was application site reaction (2% **EMSAM** vs. 0% placebo).

Adverse Events Occurring at an Incidence of 2% or More Among **EMSAM**-Treated Patients

Table 2 enumerates adverse events that occurred at an incidence of 2% or more (rounded to the nearest percent) among 817 depressed patients who received **EMSAM** in doses ranging from 3 to 12 mg/24 hours in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 2% or more of patients treated with **EMSAM** and for which the incidence in patients treated with **EMSAM** was greater than the incidence in placebo-treated patients.

Only one adverse event was associated with a reporting of at least 5% in the **EMSAM** group, and a rate at least twice that in the placebo group, in the pool of short-term, placebo-controlled studies: application site reactions (see Application Site Reactions, below). In one such study which utilized higher mean doses of **EMSAM** than that in the entire study pool, the following events met these criteria: application site reactions, insomnia, diarrhea, and pharyngitis.

These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physicians with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 2. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder With **EMSAM***

Body System/Preferred Term	EMSAM (N = 817)	Placebo (N = 668)
	(% of Patients Reporting Event)	
Body as a Whole		
Headache	18	17
Digestive		
Diarrhea	9	7
Dyspepsia	4	3
Nervous		
Insomnia	12	7
Dry Mouth	8	6
Respiratory		
Pharyngitis	3	2
Sinusitis	3	1
Skin		
Application Site Reaction	24	12
Rash	4	2

*Events reported by at least 2% of patients treated with **EMSAM** are included, except the following events, which had an incidence on placebo treatment \geq **EMSAM**: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis, and palpitations.

Application Site Reactions

In the pool of short-term, placebo-controlled major depressive disorder studies, application site reactions (ASRs) were reported in 24% of **EMSAM**-treated patients and 12% of placebo-treated patients. Most ASRs were mild or moderate in severity. None were considered serious. ASRs led to dropout in 2% of **EMSAM**-treated patients and no placebo-treated patients.

In one such study which utilized higher mean doses of **EMSAM**, ASRs were reported in 40% of **EMSAM**-treated patients and 20% of placebo-treated patients. Most of the ASRs in this study were described as erythema and most resolved spontaneously, requiring no treatment. When treatment was administered, it most commonly consisted of dermatological preparations of corticosteroids.

Male and Female Sexual Dysfunction with MAO Inhibitors

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 3 shows that the incidence rates of sexual side effects in patients with major depressive disorder are comparable to the placebo rates in placebo-controlled trials.

Table 3. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials With EMSAM

Adverse Event	EMSAM	Placebo
	IN MALES ONLY	
	(N = 304)	(N = 256)
Abnormal Ejaculation	1.0%	0.0%
Decreased Libido	0.7%	0.0%
Impotence	0.7%	0.4%
Anorgasmia	0.2%	0.0%
	IN FEMALES ONLY	
	(N = 513)	(N = 412)
Decreased Libido	0.0%	0.2%

There are no adequately designed studies examining sexual dysfunction with **EMSAM** treatment.

Vital Sign Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure), and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. In the pool of short-term, placebo-controlled major depressive disorder studies, 3.0% of **EMSAM**-treated patients and 1.5% of placebo-treated patients experienced a low systolic blood pressure, defined as a reading less than or equal to 90 mmHg with a change from baseline of at least 20 mmHg. In one study which utilized higher mean doses of **EMSAM**, 6.2% of **EMSAM**-treated patients and no placebo-treated patients experienced a low standing systolic blood pressure by these criteria.

In the pool of short-term major depressive disorder trials, 9.8% of **EMSAM**-treated patients and 6.7% of placebo-treated patients experienced a notable orthostatic change in blood pressure, defined as a decrease of at least 10 mmHg in mean blood pressure with postural change.

Weight Changes

In placebo-controlled studies (6 - 8 weeks), the incidence of patients who experienced $\geq 5\%$ weight gain or weight loss is shown in Table 4.

Table 4. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials With EMSAM

Weight Change	EMSAM	Placebo
	(N = 757)	(N = 614)
Gained $\geq 5\%$	2.1%	2.4%
Lost $\geq 5\%$	5.0%	2.8%

In these trials, the mean change in body weight among **EMSAM**-treated patients was -1.2 lbs compared to + 0.3 lbs in placebo-treated patients.

Laboratory Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with **EMSAM**.

ECG Changes

Electrocardiograms (ECGs) from **EMSAM** (N = 817) and placebo (N = 668) groups in controlled studies were compared with respect to (1) mean change from baseline in various ECG parameters, and (2) the incidence of patients meeting criteria for clinically significant changes from baseline in these variables.

No clinically meaningful changes in ECG parameters from baseline to final visit were observed for patients in controlled studies.

Other Events Observed During the Premarketing Evaluation of EMSAM

During the premarketing assessment in major depressive disorder, **EMSAM** was administered to 2036 patients in Phase III studies. The conditions and duration of exposure to **EMSAM** varied and included double-blind and open-label studies.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. All reported adverse events are included except those already listed in Table 2 or elsewhere in labeling, and those events occurring in only one patient. It is important to emphasize that although the events occurred during treatment with **EMSAM**, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent:* Chest pain, neck pain. *Infrequent:* Bacterial infection, fever, cyst, fungal infection, chills, viral infection, suicide attempt, neck rigidity, pelvic pain, photosensitivity reaction, face edema, flank pain, hernia, intentional injury, neoplasm, generalized edema, overdose. *Rare:* Body odor, halitosis, heat stroke, parasitic infection, malaise, moniliasis.

Cardiovascular System: *Frequent:* Hypertension. *Infrequent:* Vasodilatation, tachycardia, migraine, syncope, atrial fibrillation, peripheral vascular disorder. *Rare:* Myocardial infarct.

Digestive System: *Frequent:* Constipation, flatulence, anorexia, gastroenteritis, vomiting. *Infrequent:* Increased appetite, thirst, periodontal abscess, eructation, gastritis, colitis, dysphagia, tongue edema, glossitis, increased salivation, abnormal liver function tests, melena, tongue disorder, tooth caries. *Rare:* GI neoplasia, rectal hemorrhage.

Hemic and Lymphatic System: *Frequent:* Ecchymosis. *Infrequent:* Anemia, lymphadenopathy. *Rare:* Leukocytosis, leukopenia, petechia.

Metabolic and Nutritional: *Frequent:* Peripheral edema. *Infrequent:* Hyperglycemia, increased SGPT, edema, hypercholesteremia, increased SGOT, dehydration, alcohol intolerance, hyponatremia, increased lactic dehydrogenase. *Rare:* Increased alkaline phosphatase, bilirubinemia, hypoglycemic reaction.

Musculoskeletal System: *Frequent:* Myalgia, pathological fracture. *Infrequent:* Arthralgia, generalized spasm, arthritis, myasthenia, arthrosis, tenosynovitis. *Rare:* Osteoporosis.

Nervous System: *Frequent:* Agitation, paresthesia, thinking abnormal, amnesia. *Infrequent:* Leg cramps, tremor, vertigo, hypertonia, twitching, emotional lability, confusion, manic reaction, depersonalization, hyperkinesias, hostility, myoclonus, circumoral paresthesia, hyperesthesia, increased libido, euphoria, neurosis, paranoid reaction. *Rare:* Ataxia.

Respiratory System: *Frequent:* Cough increased, bronchitis. *Infrequent:* Dyspnea, asthma, pneumonia, laryngismus. *Rare:* Epistaxis, laryngitis, yawn.

Skin and Appendages: *Frequent:* Pruritus, sweating, acne. *Infrequent:* Dry skin, maculopapular rash, contact dermatitis, urticaria, herpes simplex, alopecia, vesiculobullous rash, herpes zoster, skin hypertrophy, fungal dermatitis, skin benign neoplasm. *Rare:* Eczema.

Special Senses: *Frequent:* Taste perversion, tinnitus. *Infrequent:* Dry eyes, conjunctivitis, ear pain, eye pain, otitis media, parosmia. *Rare:* Mydriasis, otitis external, visual field defect.

Urogenital System: *Frequent:* Urinary tract infection, urinary frequency, dysmenorrhea, metrorrhagia. *Infrequent:* Urinary tract infection (male), vaginitis, cystitis (female), hematuria (female), unintended pregnancy, dysuria (female), urinary urgency (male and female), vaginal moniliasis, menorrhagia, urination impaired (male), breast neoplasm (female), kidney calculus (female), vaginal hemorrhage, amenorrhea, breast pain, polyuria (female).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

EMSAM (selegiline transdermal system) is not a controlled substance.

Physical and Psychological Dependence

Several animal studies have assessed potential for abuse and/or dependence with chronic selegiline administration. None of these studies demonstrated a potential for selegiline abuse or dependence.

EMSAM has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of **EMSAM** misuse or abuse (e.g., development of tolerance, increases in dose, or drug-seeking behavior).

OVERDOSAGE

There are no specific antidotes for **EMSAM**. If symptoms of overdosage occur, immediately remove the **EMSAM** system and institute appropriate supportive therapy. For contemporary consultation on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222.

EMSAM is considered to be an irreversible MAOI at therapeutic doses and, in overdosage, is likely to cause excessive MAO-A inhibition, and may result in the signs and symptoms resembling overdosage with other non-selective, oral MAOI antidepressants [e.g., tranylcypromine (Parnate[®]), phenelzine (Nardil[®]), or isocarboxazide (Marplan[®])].

Overdosage with Non-Selective MAO Inhibition

NOTE: The following is provided for reference only; it does not describe events that have actually been observed with selegiline in overdosage. No information regarding overdose by ingestion of **EMSAM** is available.

Typical signs and symptoms associated with overdosage of non-selective MAOI antidepressants may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur, and peak effects may not be observed for 24 - 48 hours. Since death has been reported following overdosage with MAOI agents, hospitalization with close monitoring during this period is essential.

Overdosage with MAOI agents is typically associated with CNS and cardiovascular toxicity. Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, coma, rapid and irregular pulse, hypertension, hypotension and vascular collapse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin. Type and intensity of symptoms may be related to extent of the overdosage.

Treatment should include supportive measures, with pharmacological intervention as appropriate. Symptoms may persist after drug washout because of the irreversible inhibitory effects of these agents on systemic MAO activity. With overdosage, in order to avoid the occurrence of hypertensive crisis ("cheese reaction"), dietary tyramine should be restricted for several weeks beyond recovery to permit regeneration of the peripheral MAO-A isoenzyme.

DOSAGE AND ADMINISTRATION

Initial Treatment

EMSAM should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 hours. The recommended starting dose and target dose for **EMSAM** is 6 mg/24 hours.

EMSAM has been systematically evaluated and shown to be effective in a dose range of 6 mg/24 hours to 12 mg/24 hours. However, the trials were not designed to assess if higher doses are more effective than the lowest effective dose of 6 mg/24 hours. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur in dose increments of 3 mg/24 hours (up to a maximum dose of 12 mg/24 hours) at intervals of no less than 2 weeks. As with all antidepressant drugs, full antidepressant effect may be delayed.

Patients should be informed that tyramine-rich foods and beverages should be avoided beginning on the first day of **EMSAM** 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for 2 weeks after a dose reduction to **EMSAM** 6 mg/24 hours or following the discontinuation of **EMSAM** 9 mg/24 hours or 12 mg/24 hours (see WARNINGS).

Special Populations

EMSAM at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. EMSAM is not approved for use in pediatric patients.

No dosage adjustment is required for patients with mild to moderate renal or hepatic impairment. The recommended dose for elderly patients (≥ 65 years) is **EMSAM** 6 mg/24 hours daily. Dose increases, in the elderly, should be made with caution and patients should be closely observed for postural changes in blood pressure throughout treatment.

How to Use EMSAM

1. **EMSAM** should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm. A new application site should be selected with each new patch to avoid re-application to the same site on consecutive days. Patches should be applied at approximately the same time each day.
2. Apply the patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight, which could cause the patch to rub off.
3. After you have selected the site for your patch, wash the area gently and thoroughly with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
4. Just before you apply the patch, remove it from the pouch. Remove half of the protective backing and throw it away. Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers.
5. Press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface.

6. After you have applied the patch, wash your hands thoroughly with soap and water to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.
7. After 24 hours, remove the patch. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
8. Throw away the folded patch so that children and/or pets cannot reach it.
9. Wash your hands with soap and water.
10. If your patch falls off, apply a new patch to a new site and resume your previous schedule.
11. Only one **EMSAM** patch should be worn at a time.
12. Avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Maintenance Treatment

It is generally agreed that episodes of depression require several months or longer of sustained pharmacologic therapy. The benefit of maintaining depressed patients on therapy with **EMSAM** at a dose of 6 mg/24 hours after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see Clinical Efficacy Trials and INDICATIONS AND USAGE). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

HOW SUPPLIED

EMSAM (selegiline transdermal system) is supplied as 6 mg/24 hours (20 mg/20 cm²), 9 mg/24 hours (30 mg/30 cm²) and 12 mg/24 hours (40 mg/40 cm²) transdermal systems.

They are available as:

NDC 49502-900-30: 6 mg/24 hours (20 mg/20 cm²) box of 30 transdermal systems.

NDC 49502-901-30: 9 mg/24 hours (30 mg/30 cm²) box of 30 transdermal systems.

NDC 49502-902-30: 12 mg/24 hours (40 mg/40 cm²) box of 30 transdermal systems.

STORAGE AND DISPOSAL

Store at 20° to 25° C (68° to 77° F). [See USP Controlled Room Temperature.] Do not store outside of the sealed pouch. Apply immediately upon removal from the protective pouch. Discard used **EMSAM** in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

DISTRIBUTED BY:

Dey, L.P.

Napa, CA 94558

MANUFACTURED FOR:

Somerset

Pharmaceuticals, Inc.

Morgantown, WV 26505

MAY 2009

EMSAM:PIR7

03-943-00

MEDICATION GUIDE EMSAM[®] [EM SAM]

GENERIC NAME: SELEGILINE TRANSDERMAL SYSTEM

Read this Medication Guide carefully before you start using **EMSAM** and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about **EMSAM**, ask your doctor or pharmacist.

IMPORTANT: Be sure to read the section of this Medication Guide beginning with “What is the most important information I should know about EMSAM?” It contains important information about certain changes in diet that might be needed, other medications to avoid, and other important information about this medication. It immediately follows the next section called Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions.

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illnesses

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
 - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
 - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
 - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

ABOUT USING ANTIDEPRESSANTS IN CHILDREN AND TEENAGERS

EMSAM at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. EMSAM is not approved for use in pediatric patients.

What is the most important information I should know about EMSAM?

- EMSAM (selegiline transdermal system) contains a medicine called a monoamine oxidase inhibitor, also called a MAOI. MAOI medicines, including EMSAM, can cause a sudden, large increase in blood pressure (hypertensive crisis) if you eat foods and drinks that contain high amounts of tyramine. A hypertensive crisis can be a life-threatening condition. See "What are the possible side effects of EMSAM?" for signs and symptoms of a hypertensive crisis.
- EMSAM comes in three different doses and patch sizes:
 - a 6 mg/24 hours patch
 - a 9 mg/24 hours patch
 - a 12 mg/24 hours patch
- **You must avoid (not eat or drink) certain foods and drinks while using EMSAM 9 mg/24 hours and EMSAM 12 mg/24 hours patches and for 2 weeks after stopping EMSAM 9 mg/24 hours and EMSAM 12 mg/24 hours patches.** (The table below lists these foods and drinks.²) The table also lists foods and drinks that are okay to eat and drink while using EMSAM 9 mg/24 hours and EMSAM 12 mg/24 hours patches.
- **You do not have to make any diet changes with the EMSAM 6 mg/24 hours patch.**

Type of Food and Drink	Tyramine-Rich Foods and Drinks to Avoid	Acceptable Foods and Drinks, Containing No or Little Tyramine
<u>Meat, Poultry, and Fish</u>	<ul style="list-style-type: none"> • Air dried, aged and fermented meats, sausages and salamis • Pickled herring • Any spoiled or improperly stored meat, poultry, and fish. <p>These are foods that have a change in color, odor, or become moldy.</p> <ul style="list-style-type: none"> • Spoiled or improperly stored animal livers 	<ul style="list-style-type: none"> • Fresh meat, poultry, and fish, including fresh processed meats (such as lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
<u>Vegetables</u>	<ul style="list-style-type: none"> • Broad bean pods (fava bean pods) 	<ul style="list-style-type: none"> • All other vegetables
<u>Dairy (milk products)</u>	<ul style="list-style-type: none"> • Aged cheeses 	<ul style="list-style-type: none"> • Processed cheeses, mozzarella, ricotta cheese, cottage cheese, and yogurt
<u>Drinks</u>	<ul style="list-style-type: none"> • All tap beers and other beers that have not been pasteurized 	<ul style="list-style-type: none"> • As with other antidepressants, concomitant use of alcohol with EMSAM is not recommended. (Bottled and canned beers and wines contain little or no tyramine.)
<u>Other</u>	<ul style="list-style-type: none"> • Concentrated yeast extract (such as Marmite) • Sauerkraut • Most soybean products (including soy sauce and tofu) • Over-the-counter supplements containing tyramine 	<ul style="list-style-type: none"> • Brewer's yeast, baker's yeast • Soy milk • Pizzas from commercial chain restaurants prepared with cheeses low in tyramine

- All foods you eat must be fresh or properly frozen.
- Avoid foods when you do not know their storage conditions.

- **EMSAM can cause serious and potentially life-threatening reactions if used with certain other medicines. Do not take the following medicines while using EMSAM, and for 2 weeks after stopping EMSAM:**

- # other medicines to treat depression (antidepressants) including other MAOI medicines
- # medicine which contains selegiline (such as Eldepryl®)
- # St. John's wort (a herbal supplement)
- # Demerol® (meperidine), or medicines that contain meperidine (a narcotic pain medicine) or the pain medicines tramadol, methadone, or propoxyphene
- # Tegretol® (carbamazepine), or other medicines that contain carbamazepine (a seizure medicine)
- # Trileptal® (oxcarbazepine), or other medicines that contain oxcarbazepine (a seizure medicine)
- # Cold or cough preparations that contain dextromethorphan
- # Flexeril® or other medicines that contain cyclobenzaprine (a medicine used to treat muscle spasms)
- # decongestant medicines, found in many products to treat cold symptoms
- # over-the-counter diet pills or herbal weight-loss products
- # any herbal or dietary supplement that contains tyramine
- # medicines called amphetamines, also called stimulants or "uppers"
- # BuSpar® (buspirone HCl), an anxiety medicine

Some of these medicines will have to be stopped for at least a week before you can start using EMSAM.

2

Adapted from K.I. Shulman, S.E. Walker, Psychiatric Annals 2001; 31:378-384

What is EMSAM?

EMSAM is a skin patch (transdermal system) used to treat major depression. The skin patch delivers the medicine through your skin and into your bloodstream.

EMSAM has not been studied for the treatment of depression in children under 18 years of age.

Who should not use EMSAM?

Do not use EMSAM (selegiline transdermal system) if you are:

- **taking certain other medicines.** See "What is the most important information I should know about EMSAM?"
- **allergic to anything in EMSAM.** See the end of this Medication Guide for a complete list of ingredients in **EMSAM**.

What should I tell my doctor before starting EMSAM?

Tell your doctor about all your medical conditions, including if you:

- **have any heart problems**
- **have or had manic episodes** (a mental condition that causes "high" moods)
- **have or had seizures** (convulsions or "fits")
- **tend to get dizzy or faint**
- **are pregnant or planning to become pregnant.** It is not known if **EMSAM** can harm your unborn baby.
- **are breast-feeding.** It is not known if **EMSAM** passes into your milk or if it can harm your baby.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. **EMSAM can cause a serious and life-threatening reaction if used with certain other medicines.** See "What is the most important information I should know about EMSAM?"

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist. Do not take any new medicine while using EMSAM, and for 2 weeks after you stop using it, before talking with your doctor.

How should I use EMSAM?

See the end of this Medication Guide for "How to Use and Apply an EMSAM Patch".

- Use **EMSAM** exactly as prescribed by your doctor. **Use only one patch at a time.** Change the patch once a day (every 24 hours). Choose a time of day that works best for you.
- Your doctor will prescribe a dose of **EMSAM** (selegiline transdermal system) based on your condition. Your doctor may change your dose if needed.

- Talk to your doctor often about your condition. You may notice an improvement in your condition with **EMSAM** therapy after several weeks. **Do not stop or change your treatment with EMSAM without talking to your doctor.**
- **Make sure you do not eat foods or drink beverages that contain high amounts of tyramine while using EMSAM 9 mg/24 hours or EMSAM 12 mg/24 hours patches, and for 2 weeks after you stop using them.**
- If you use more than one **EMSAM patch at a time**, remove **EMSAM patches** right away and call your doctor or local Poison Control Center.
- Avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.
- Tell your doctor if you plan to have surgery. Also, tell your surgeon that you take **EMSAM**. **EMSAM** should be stopped 10 days before you have elective surgery.

What should I avoid while using EMSAM?

- **You must not eat foods or drink beverages that contain high amounts of tyramine while using EMSAM 9 mg/24 hours and 12 mg/24 hours patches.** You do not have to make any diet changes with the **EMSAM 6 mg/24 hours patch**. See “**What is the most important information I should know about EMSAM?**”
- **Do not take other medicines while using EMSAM or for 2 weeks after you stop using it unless your doctor has told you it is okay.** See “**What is the most important information I should know about EMSAM?**”
- **Do not drive or operate dangerous machinery until you know how EMSAM affects you.** **EMSAM may reduce your judgment, ability to think, or coordination.**
- **Drinking alcoholic beverages is not recommended while using EMSAM.**

What are the possible side effects of EMSAM?

EMSAM:

- **can cause a sudden, large increase in blood pressure (“hypertensive crisis”)** if you eat certain foods and drinks during treatment. See “**What is the most important information I should know about EMSAM?**” **A hypertensive crisis can lead to stroke and death.** Symptoms of a hypertensive crisis include the sudden onset of severe headache, nausea, stiff neck, a fast heartbeat or a change in the way your heart beats (palpitations), a lot of sweating, and confusion. **If you suddenly have these symptoms, get medical care right away.**
- **can cause serious and potentially life-threatening reactions if used with certain other medicines.** See “**What is the most important information I should know about EMSAM?**”
- **may worsen your depression, give you suicidal thoughts, or cause unusual changes in behavior.** Call your doctor right away if you feel worse with **EMSAM**.
- **may cause a mental condition called mania or hypomania** (mental condition which causes high moods) in people who have a history of mania.
- **can cause low blood pressure.** Lie down if you feel dizzy, faint, or lightheaded. Change your position slowly if low blood pressure is a problem for you. Tell your doctor if you have these symptoms. You may need a lower dose of **EMSAM**.

The most common side effect of **EMSAM** is a skin reaction where the patch is placed. You may see mild redness at the site when a patch is removed. This redness should go away within several hours after removing the patch. If irritation or itching continues, tell your doctor.

These are not all the side effects of **EMSAM**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store EMSAM?

- Store **EMSAM** at 20° to 25° C (68° to 77° F).
- Store **EMSAM** in its sealed pouch until use.
- **Keep EMSAM and all medicines out of the reach of children and away from pets.**

General information about EMSAM

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not give **EMSAM** to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about **EMSAM**. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about **EMSAM** that is written for health professionals.

For more information, call 1-866-367-2678 or visit www.EMSAM.com

What are the ingredients in EMSAM?

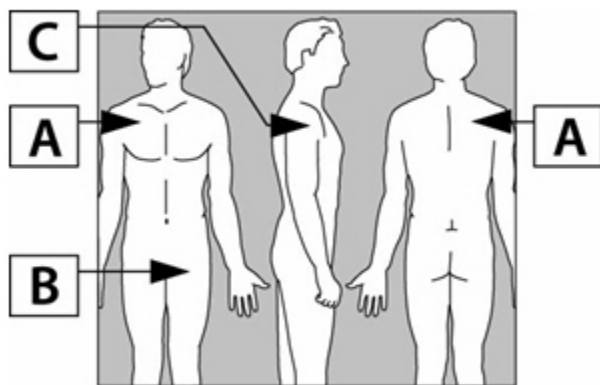
Active Ingredient: Selegiline

Inactive Ingredients: acrylic adhesive, ethylene vinyl acetate, polyethylene, polyester, polyurethane, and silicone coated polyester

How to Use and Apply an EMSAM Patch

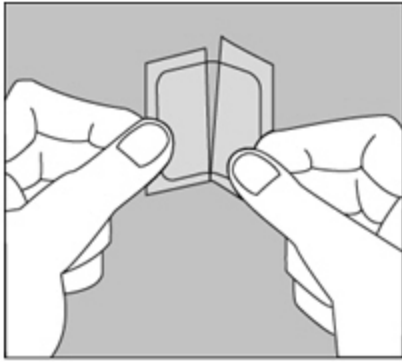
Read these instructions carefully before you apply EMSAM (selegiline transdermal system). Ask your doctor or pharmacist about anything you do not understand.

- Apply a new **EMSAM** patch every day (24 hours).
- **Wear only one EMSAM patch at a time.** Wear one **EMSAM** patch all the time until it is time to apply a new one.
- Remove a used patch before applying a new one.
- Change the patch at the same time each day.
- Apply an **EMSAM** patch to dry, smooth skin on your (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) to the outer surface of the upper arm. Choose a new site each time you change your patch. Do not use the same site 2 days in a row. (See Picture 1 for skin sites that may be used.)

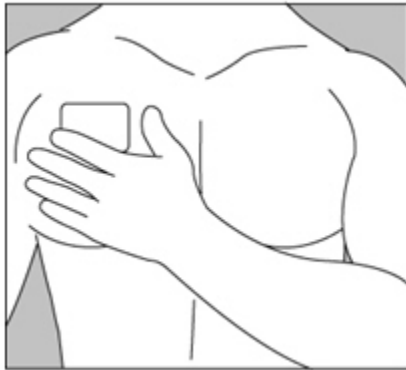


Picture 1. Skin sites for EMSAM patch. (Do not use more than one patch at a time.)

- Apply an **EMSAM** patch to an area of skin that is not hairy, oily, irritated, broken, scarred, or calloused. Do not place the patch where your clothing is tight, which could cause the patch to rub off.
- After you have selected the site for your patch, wash the area gently and well with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
- Just before you apply the patch, remove it from its sealed pouch. **Do not keep or store the patch outside of the sealed pouch. Never cut an EMSAM patch into smaller pieces to use.**
- Remove half of the protective backing and throw it away. (See Picture 2.) Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers. With your fingertips, press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface. (See Picture 3.)



Picture 2. Removing the protective backing from an EMSAM patch.



Picture 3. Applying an EMSAM patch.

- After you have applied the patch, wash your hands well with soap and water to remove any medicine that may have gotten on them. **Do not touch your eyes until after you have washed your hands.**
- After 24 hours, remove the patch slowly and carefully to avoid damaging the skin. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
- Throw away the folded patch so that children and pets cannot reach it. This patch still contains some medicine and could harm a child or pet.
- Gently wash the old application site with warm water and a mild soap to remove any sticky material (adhesive) that stays on your skin after removing the patch. A small amount of baby oil may also be used to remove any adhesive. You may need to use a medical adhesive removal pad that you can get from your pharmacist. Alcohol or other dissolving liquids such as nail polish remover may cause skin irritation and should not be used.
- Wash your hands with soap and water.
- If the patch becomes loose, press it back in place. If your **EMSAM** (selegiline transdermal system) patch falls off, apply a new **EMSAM** patch to a new site and resume your normal schedule for changing patches.
- If you forget to change your patch after 24 hours, remove the old patch, put on a new patch in a different area and continue to follow your original schedule.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Dey, L.P.

Napa, CA 94558

MANUFACTURED FOR:

Somerset

Pharmaceuticals, Inc.

Morgantown, WV 26505

*Prozac[®] is a registered trademark of Eli Lilly and Company

*Zoloft[®] is a registered trademark of Pfizer Pharmaceuticals

*Anafranil[®] is a registered trademark of Mallinckrodt Inc.

*Demerol[®] is a registered trademark of Sanofi

*Eldepryl[®] is a registered trademark of Somerset Pharmaceuticals

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*BuSpar[®] is registered trademark of Bristol-Myers Squibb Company

MAY 2009

EMSAM:PLR7

03-944-00

PRINCIPAL DISPLAY PANEL - 6 mg/24 h

NDC-49502-900-30

EACH UNIT DOSE PACKAGE IS NOT CHILD RESISTANT

Rx only

EMSAM[®]

(selegiline transdermal system)

6 mg/24 h

FOR TRANSDERMAL USE ONLY

Patient: Read enclosed Medication Guide.

Pharmacist: Dispense with enclosed
Medication Guide.

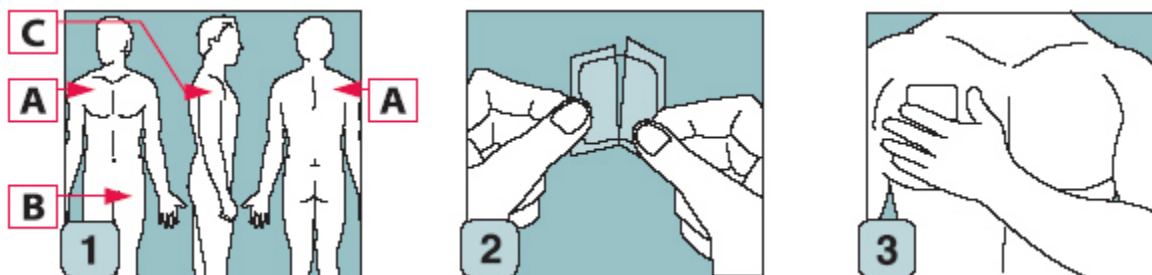
30 TRANSDERMAL

SYSTEMS

INSTRUCTIONS FOR APPLICATION

1. Select and prepare an appropriate site on the (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) outer surface of the upper arm, as directed in the enclosed Medication Guide.
2. Bend both sides of the clear peelable liner. Peel off one strip only of the clear liner. Avoid touching the sticky side of the transdermal system.
3. Apply sticky side of the transdermal system to the chosen skin site. Remove remaining strip, gently roll remaining part onto skin, and press transdermal system firmly in place with the tips of your fingers.

For more detailed instructions, read enclosed Medication Guide.



Dosage: Apply one (1) transdermal system every 24 hours. Read enclosed Medication Guide.

Each transdermal system has a release rate of 6 mg selegiline per 24 hour period. Wear only one transdermal system at a time.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

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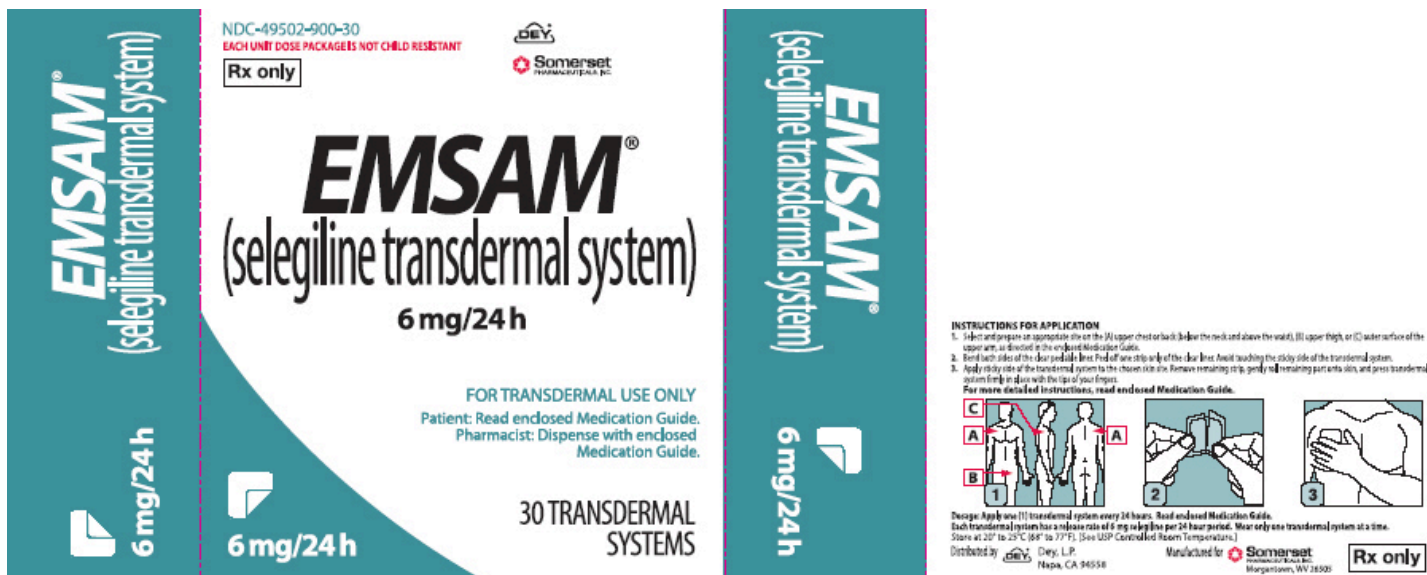
Manufactured for

Somerset

Pharmaceuticals, Inc.

Morgantown, WV 26505

Rx only



PRINCIPAL DISPLAY PANEL - 9 mg/24 h

NDC-49502-901-30

EACH UNIT DOSE PACKAGE IS NOT CHILD RESISTANT

Rx only

EMSAM[®]

(selegiline transdermal system)

9 mg/24 h

Important: Do not eat certain foods.

Read enclosed Medication Guide.

FOR TRANSDERMAL USE ONLY

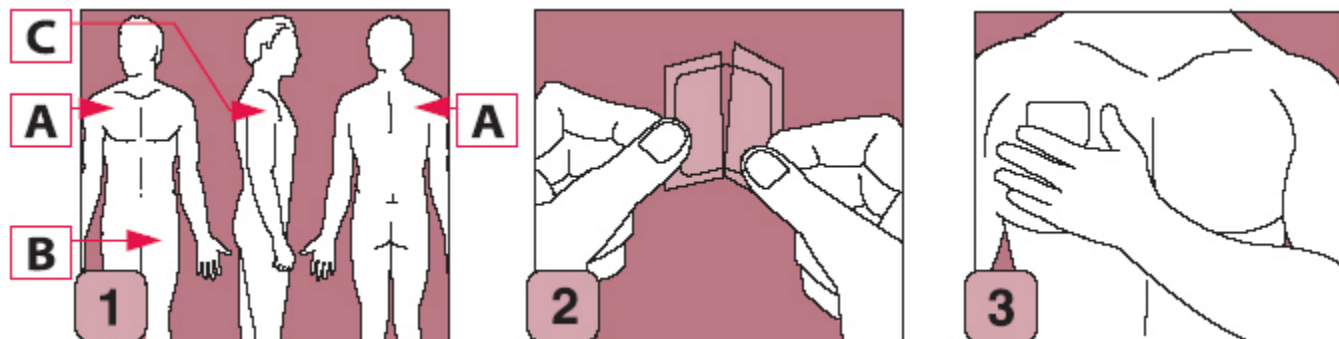
Pharmacist: Dispense with enclosed Medication Guide.

30 TRANSDERMAL SYSTEMS

INSTRUCTIONS FOR APPLICATION

1. Select and prepare an appropriate site on the (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) outer surface of the upper arm, as directed in the enclosed Medication Guide.
2. Bend both sides of the clear peelable liner. Peel off one strip only of the clear liner. Avoid touching the sticky side of the transdermal system.
3. Apply sticky side of the transdermal system to the chosen skin site. Remove remaining strip, gently roll remaining part onto skin, and press transdermal system firmly in place with the tips of your fingers.

For more detailed instructions, read enclosed Medication Guide.



Dosage: Apply one (1) transdermal system every 24 hours. Read enclosed Medication Guide.

Each transdermal system has a release rate of 9 mg selegiline per 24 hour period. Wear only one transdermal system at a time.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

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Pharmaceuticals, Inc.
Morgantown, WV 26505
Rx only

EMSAM[®]
(selegiline transdermal system)
9 mg/24h

Important: Do not eat certain foods. Read enclosed Medication Guide.

NDC-49502-901-30
EACH UNIT DOSE PACKAGE IS NOT CHILD RESISTANT
Rx only

EMSAM[®]
(selegiline transdermal system)
9 mg/24h

Important: Do not eat certain foods. Read enclosed Medication Guide.

FOR TRANSDERMAL USE ONLY
Pharmacist: Dispense with enclosed Medication Guide.

30 TRANSDERMAL SYSTEMS

INSTRUCTIONS FOR APPLICATION

1. Select and prepare an appropriate site on the (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) outer surface of the upper arm, as directed in the enclosed Medication Guide.
2. Bend both sides of the clear peelable liner. Peel off one strip only of the clear liner. Avoid touching the sticky side of the transdermal system.
3. Apply sticky side of the transdermal system to the chosen skin site. Remove remaining strip, gently roll remaining part onto skin, and press transdermal system firmly in place with the tips of your fingers.

For more detailed instructions, read enclosed Medication Guide.

Warnings: Apply one (1) transdermal system every 24 hours. Read enclosed Medication Guide. Each transdermal system has a release rate of 9 mg selegiline per 24 hour period. Wear only one transdermal system at a time. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

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Napa, CA 94558

Manufactured for **Somerset Pharmaceuticals, Inc.**
Morgantown, WV 26505

Rx only

PRINCIPAL DISPLAY PANEL - 12 mg/24 h

NDC-49502-902-30

EACH UNIT DOSE PACKAGE IS NOT CHILD RESISTANT

Rx only

EMSAM[®]

(selegiline transdermal system)

12 mg/24 h

Important: Do not eat certain foods.

Read enclosed Medication Guide.

FOR TRANSDERMAL USE ONLY

Pharmacist: Dispense with enclosed

Medication Guide.

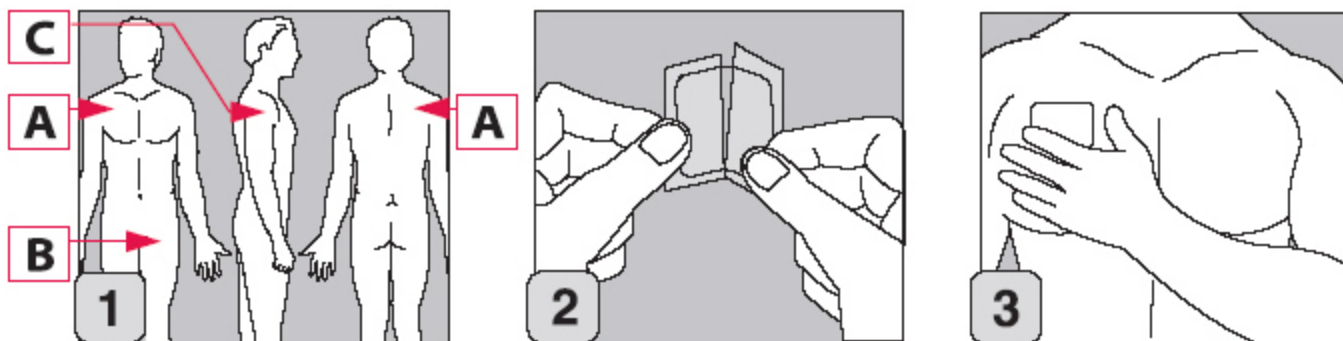
30 TRANSDERMAL

SYSTEMS

INSTRUCTIONS FOR APPLICATION

1. Select and prepare an appropriate site on the (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) outer surface of the upper arm, as directed in the enclosed Medication Guide.
2. Bend both sides of the clear peelable liner. Peel off one strip only of the clear liner. Avoid touching the sticky side of the transdermal system.
3. Apply sticky side of the transdermal system to the chosen skin site. Remove remaining strip, gently roll remaining part onto skin, and press transdermal system firmly in place with the tips of your fingers.

For more detailed instructions, read enclosed Medication Guide.



Dosage: Apply one (1) transdermal system every 24 hours. Read enclosed Medication Guide.

Each transdermal system has a release rate of 12 mg selegiline per 24 hour period. Wear only one transdermal system at a time.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

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Pharmaceuticals, Inc.

Morgantown, WV 26505

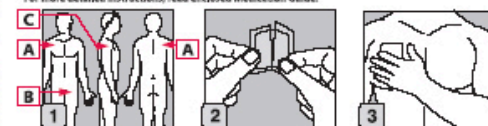
Rx only



INSTRUCTIONS FOR APPLICATION

1. Subject and prepare an application site on the (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) outer surface of the upper arm, as directed in the enclosed Medication Guide.
2. Peel both sides of the clear peelable lines. Peel off one side of the clear liner. Avoid touching the sticky side of the transdermal system.
3. Apply sticky side of the transdermal system to the chosen skin site. Remove remaining area, gently roll remaining part onto skin, and press transdermal system firmly in place with the tips of your fingers.

For more detailed instructions, read enclosed Medication Guide.



Dosage: Apply one (1) transdermal system every 24 hours. Read enclosed Medication Guide. Each transdermal system has a release rate of 12 mg selegiline per 24 hour period. Wear only one transdermal system at a time. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

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Rx only

PRINCIPAL DISPLAY PANEL - 6 mg/24 h Physician Sample

NDC-49502-900-05

EACH UNIT DOSE PACKAGE IS NOT CHILD RESISTANT

Rx only

EMSAM®

(selegiline transdermal system)

6 mg/24 h

PHYSICIAN SAMPLE - NOT FOR SALE

Please visit www.EMSAM.com

FOR TRANSDERMAL USE ONLY

Patient: Read enclosed Medication Guide.

Dispenser: Dispense with enclosed

Medication Guide.

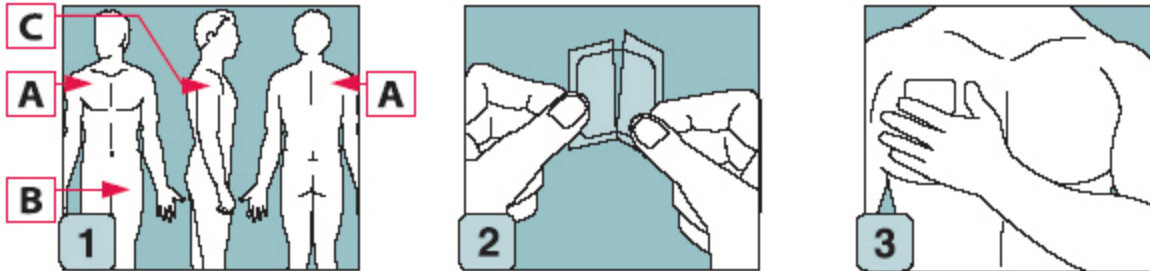
5 TRANSDERMAL

SYSTEMS

INSTRUCTIONS FOR APPLICATION

1. Select and prepare an appropriate site on the (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) outer surface of the upper arm, as directed in the enclosed Medication Guide.
2. Bend both sides of the clear peelable liner. Peel off one strip only of the clear liner. Avoid touching the sticky side of the transdermal system.
3. Apply sticky side of the transdermal system to the chosen skin site. Remove remaining strip, gently roll remaining part onto skin, and press transdermal system firmly in place with the tips of your fingers.

For more detailed instructions, read enclosed Medication Guide.



Dosage: Apply one (1) transdermal system every 24 hours. Read enclosed Medication Guide.

Each transdermal system has a release rate of 6 mg selegiline per 24 hour period. Wear only one transdermal system at a time.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

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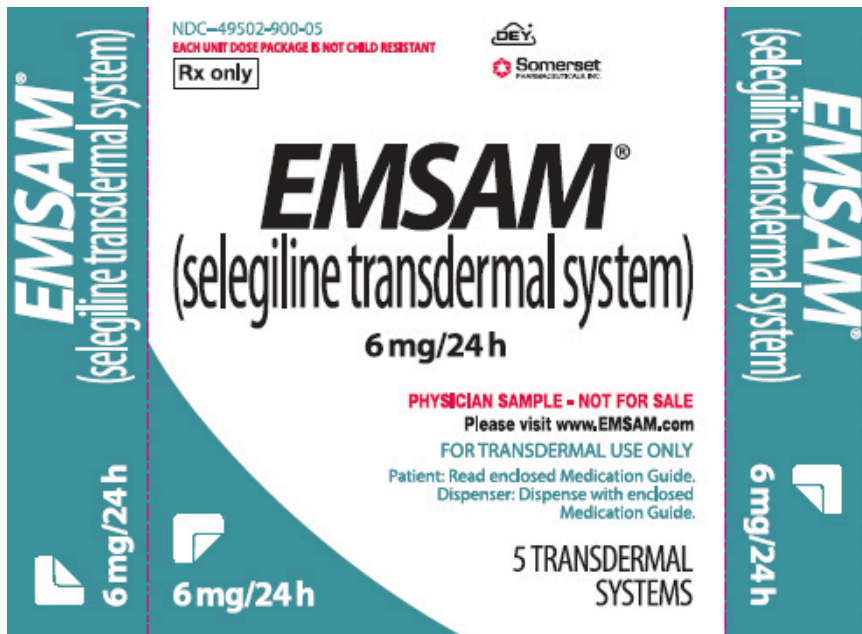
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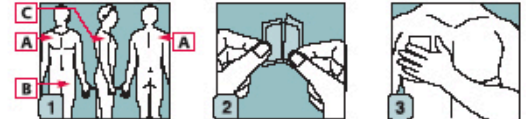
Rx only



INSTRUCTIONS FOR APPLICATION

1. Select and prepare an appropriate site on the (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) outer surface of the upper arm, as directed in the enclosed Medication Guide.
2. Bend both sides of the clear peelable liner. Peel off one strip only of the clear liner. Avoid touching the sticky side of the transdermal system.
3. Apply sticky side of the transdermal system to the chosen skin site. Remove remaining strip, gently roll remaining part onto skin, and press transdermal system firmly in place with the tips of your fingers.

For more detailed instructions, read enclosed Medication Guide.



Dosage: Apply one (1) transdermal system every 24 hours. Read enclosed Medication Guide. Each transdermal system has a release rate of 6 mg selegiline per 24 hour period. Wear only one transdermal system at a time.

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